Clinical Commentary Review

Food Protein-Induced Enterocolitis Syndrome (FPIES): Current Management Strategies and Review of the Literature

Kirsi M. Järvinen, MD, PhD[a], and Anna Nowak-Węgrzyn, MD[b] *Albany and New York, NY*

Food protein-induced enterocolitis syndrome (FPIES) is a non−IgE-mediated gastrointestinal food hypersensitivity that manifests as profuse, repetitive vomiting, often with diarrhea, leading to acute dehydration and lethargy or weight loss and failure to thrive if chronic. FPIES is elicited most commonly by milk and soy proteins; however, rice, oat, and other solid foods may also elicit FPIES. Certain FPIES features overlap with food protein-induced enteropathy and proctocolitis, whereas others overlap with anaphylaxis. FPIES is not well recognized among pediatricians and emergency department physicians; the affected children are often mismanaged as having acute viral gastrointestinal illness, sepsis, or surgical disease, delaying diagnosis of FPIES for many months. The aim of this review is to provide case-driven presentation of the features of FPIES. Although randomized clinical trials on management options are missing, the relevant current literature and authors' experience are reviewed in detail. © 2013 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol: In Practice 2013;■:■-■)

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Food protein-induced enterocolitis syndrome (FPIES) is a non−IgE-mediated gastrointestinal food hypersensitivity that manifests as profuse, repetitive vomiting, often with diarrhea, leading to acute dehydration and lethargy or weight loss and failure to thrive if chronic[1] (Box 1; see also Table E1 in this article's Online Repository at www.jaci-inpractice.org). Here, we present the clinical features according to the age of onset and trigger food [cow's milk (CM) and soy FPIES versus solid food FPIES versus multiple foods FPIES] as well as according to acute or chronic presentation.

CLINICAL FEATURES

Age of onset and trigger foods

CM/soy FPIES. A common presentation of FPIES is profuse, repetitive emesis and diarrhea in a young infant fed with CM or soy formula[2-4] (Box 1; see also Table E2 in this article's Online Repository at www.jaci-inpractice.org). Classic FPIES begins in early infancy within the 3 months of life (but up to 1 year of age), usually 1 to 4 weeks after introduction of formula. In the Israeli population-based birth cohort, the median age of FPIES onset was 30 days; all infants presented younger than 6 months of age.[5] Delayed introduction of CM or soy in breast-fed infants may result in a later onset. FPIES to CM and soy present in the breast milk in exclusively breast-fed infants is extremely rare, although reported in two case studies (see "Breast-feeding").[6,7]

Solid foods FPIES. FPIES may be induced by solid foods, with age at onset later than that of CM and soy FPIES, because solid foods are usually introduced between 4 and 7 months of age.[2,8] Rice is the most common solid food that induces FPIES,[9] followed by oat, barley, chicken, turkey, egg white, green pea, peanut, sweet potato, white potato, corn, fruit protein, fish, and mollusks.[10-15] The common triggers in FPIES, rice and oat and vegetables, are considered to be hypoallergenic for IgE-mediated food allergy and are usually the first solids introduced into an infant's diet.

Natural history of FPIES appears to be modified by delaying introduction of foods with higher allergenic potential (eg, egg) or from the same food group (eg, wheat in rice FPIES). Egg is rarely reported as an FPIES trigger. However, in an Australian cohort of 38 patients, egg FPIES occurred in 10%.[16] In addition, among 10 infants with CM or soy FPIES, 3 (30%) developed egg FPIES when exposed to egg at a median age of 5.5 months.[17] Wheat FPIES has been reported only twice,[18,19] presumably because of significantly delayed introduction of wheat to the diet of infants with FPIES.[10,20] FPIES onset after 1 year of age is rare, although FPIES to fish and shellfish (including mollusks and crustaceans) has been observed in older children and adults.[8,21]

Multiple food FPIES: CM and soy FPIES. Up to 50% of the patients react to both CM and soy in the US studies.[10,22-24] Studies from Australia and Israel reported no patients reacting to both CM and soy.[2,5] These differences may reflect selection bias

[a]Division of Allergy and Immunology, Albany Medical College, Albany, NY
[b]Division of Pediatric Allergy & Immunology and Jaffe Institute for Food Allergy, The Mount Sinai School of Medicine, New York, NY

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Corresponding author: Kirsi M. Järvinen, MD, PhD, Division of Allergy and Immunology, Albany Medical College, 47 New Scotland Ave, MC 151, Albany, NY 12208. E-mail: jarvink@mail.amc.edu.

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Abbreviations used
APT- Atopy patch test
CM- Cow's milk
FPIES- Food protein-induced enterocolitis
OFC- Oral food challenge
SPT- Skin prick test

with more severe cases reported from the allergy referral populations in the US studies, different feeding practices, genetic factors, or lack of exposure to both CM and soy because of feeding with a hypoallergenic formula after a diagnosis of FPIES to CM or soy.

Multiple food FPIES: CM/soy FPIES and solid foods FPIES. Approximately one-third of infants with CM or soy FPIES develop solid foods FPIES, commonly caused by rice and oat, the grains typically introduced at weaning.[10,20] In the US study, 50% of infants reacted to more than one grain: rice, oat, or barley.[10] In contrast, 1 of 14 Australian infants with rice FPIES reacted to oat.[9] There is a variably high rate of multiple foods in solid FPIES. Eighty percent of infants with solid foods FPIES reacted to more than one food, and 65% were previously diagnosed with CM and/or soy FPIES.[10] However, in an Australian study, only 17% of infants with solid foods FPIES reacted to multiple foods.[2]

Acute symptoms

FPIES may present acutely, after the food has been removed from the diet and then re-introduced, or if it is ingested intermittently (Box 1, Case 1). Severe, projectile, repetitive (up to 15-20 episodes) emesis starts within 1 to 3 hours after food ingestion, accompanied by lethargy with pallor and ashen appearance. Diarrhea may follow within 2 to 10 hours (mean onset, 5 hours), especially in severe reactions. Stool may contain blood, mucous, sheets of leukocytes and eosinophils, and have increased carbohydrate content.[25] Peripheral blood neutrophil counts are usually elevated, peaking at 6 hours. In 63% of those with a recorded white blood cell count, thrombocytosis ($>500 \times 10^9$/L) was seen.[2]

Chronic symptoms

FPIES may be chronic while the food is a staple of the diet, such as with CM or soy formula in infants[25] (Box 1, Case 1). Chronic FPIES applies to situations when the culprit food is introduced early in life and every day. This can present as intermittent emesis, bloody diarrhea, lethargy, dehydration requiring intravenous hydration, abdominal distension, weight loss/failure to thrive, and metabolic acidosis that may begin within the first days of life.[25-28] Laboratory studies show anemia, hypoalbuminemia, and an elevated white blood cell count with a left shift and eosinophilia. Methemoglobulinemia was reported in approximately one-third of infants with severe reactions and acidemia; some required methylene blue and bicarbonate treatment.[26] Intramural gas was seen on abdominal x-rays, prompting a diagnosis of necrotizing enterocolitis. Overall, approximately 75% of infants with FPIES appear seriously ill; 15% develop hypotension and require hospitalization.[5] Symptoms improve with food elimination and bowel rest within several days and recur acutely on food reintroduction.

EPIDEMIOLOGY

Approximately 40% of CM-protein hypersensitivity in young children are due to non-IgE, T-cell–mediated gastrointestinal immune reactions to CM proteins.[20] The prevalence of FPIES is unknown. The only population-based birth cohort study in Israel reported CM FPIES in 0.34% of 13,019 infants, compared with 0.5% of IgE-mediated CM allergy diagnosed in the first year of life.[5] FPIES is slightly more common in boys (52%-60%).[2,5,10] Approximately 30% of infants with FPIES have atopic diseases, such as atopic dermatitis (25%-65%), asthma (3%-20%), or allergic rhinitis (20%).[2,9,11] Family history of atopy is present in 40% to 80% of patients, including food allergy in approximately 20%.[11] However, no familial cases of FPIES have been reported.[10,23]

PATHOPHYSIOLOGY

The pathophysiology of FPIES remains obscure. Antigen-specific T cells and proinflammatory cytokines that modify intestinal barrier permeability may play a role. Ingestion of food allergens may cause local inflammation, leading to increased intestinal permeability and fluid shift.[29] Systemic food-specific IgE antibodies are typically absent in FPIES. Intestinal mucosal IgE antibody may facilitate antigen uptake and intestinal inflammation, but this requires further study.[29]

DIAGNOSIS

Diagnosis is based on the history, symptoms, exclusion of other causes, and an oral food challenge (OFC). It is harder to make the correct diagnosis with the chronic form of FPIES. In infants with chronic symptoms, hypoalbuminemia and weight gain of <10 g/day were identified as independent predictors of CM FPIES.[30] In chronic FPIES, food elimination for 2 weeks, followed by a supervised OFC may be necessary for a conclusive diagnosis because of the nonspecific nature of the FPIES symptoms. Infants often present with multiple reactions and extensive evaluations before the diagnosis of FPIES is considered, especially when FPIES is caused by solid foods.[2,11] The nonspecific symptoms and lack of definitive diagnostic tests contribute to a delay in diagnosis.

Allergy tests

Most patients have negative skin prick tests (SPTs) and undetectable serum food-specific IgE. In total, approximately 21% with solid FPIES and 18% to 30% with CM or soy FPIES have detectable food-specific IgE.[5,10,23] Atopy patch test (APT) was evaluated in 19 infants aged 5 to 30 months with challenge-confirmed FPIES.[24] APTs predicted the outcomes in 28 of 33 OFCs; all positive OFCs had a positive APT. These results have not been confirmed by other studies; thus, further evaluation of APT in the diagnosis of FPIES is needed. We performed APTs in 25 children before 38 follow-up OFCs and found sensitivity of 12%, specificity of 86%, positive predictive value of 40%, and negative predictive value of 55%. These results indicate that APT had poor utility in predicting tolerance development in FPIES.[31]

Fecal tests

In chronic diarrhea, stool examination may show nonspecific findings, such as occult blood, neutrophils, eosinophils, Charcot-Leyden crystals, and reducing substances.[30]

Case 1. Chronic and acute manifestations in an infant with CM FPIES

A full-term, healthy female infant was exclusively breast-fed from birth. At 4 weeks of age, CM-based formula was supplemented, and within 2 weeks the baby developed intermittent emesis, poor weight gain, and stools with small specks of fresh blood. Exclusive breast-feeding was resumed. At 12 weeks of age, a single feeding with CM-based formula within 90 minutes elicited repetitive, projectile emesis and lethargy but no other symptoms. In the emergency department (ED) sepsis workup, toxicology, and metabolic screenings were performed. Complete blood count (CBC) showed elevated white blood count with a left shift. She was placed on intravenous fluids and antibiotics for a presumed infection. Emesis stopped with intravenous fluid resuscitation, but she passed several loose, watery stools with visible fresh blood on the first day in the hospital. The results of all laboratory diagnostic tests were within normal limits. CM allergy was suspected, and the infant was discharged home on an extensively hydrolyzed casein-based formula, which was tolerated. She was thriving and developing well. Fruits, vegetables, and grains were introduced to her diet between 5 and 7 months of age. At 9 months of age a jar of baby food that contained cheese was given to her by mistake. She started to vomit repeatedly and forcefully within 2 hours and became lethargic and appeared ashen-gray. In the ED she recovered with intravenous fluid resuscitation. She resumed strict CM avoidance. SPTs with CM, soy, egg white, fish, and nuts were negative. After 1 year of age, it was discovered that she had been tolerating soy protein in commercial foods on a regular basis, and soy beverage was slowly and gradually introduced to her diet at home, followed by egg, fish, and nuts.

Case 2. OFC in CM FPIES

The child described in the Case 1 was maintained on a strict CM protein avoidance until 3 years of age. She had had no interim reactions or exposures to CM. At 3 years of age, SPT to milk became positive at 3/5 mm (wheal/erythema), but serum CM-specific IgE was undetectable. She was referred for an oral milk challenge to evaluate for possible resolution of FPIES. She was admitted to an inpatient unit, and a peripheral intravenous line was placed in her arm. Baseline CBC with differential was obtained before the onset of feeding. The total amount of CM was calculated according to her weight, 0.3 mg protein/kg. Nonfat, dried milk powder was mixed with 100 mL of soy beverage that she has been tolerating at home. She was fed 3 equal servings every 15 minutes. After 2 hours, she complained of belly pain, stopped playing, and curled up in bed. Shortly thereafter, she threw up 4 times small amounts of liquid within 30 minutes. Her heart rate increased from baseline, but blood pressure remained stable. She was given a normal saline fluid bolus (10 mL/kg body weight) and a single dose of methylprednisolone (1 mg/kg body weight). Her emesis stopped, and abdominal pain subsided within 30 minutes. After an hour, her behavior slowly returned to baseline, and she tolerated clear liquids, followed by a light meal. She voided but had no bowel movement. She was observed for 6 hours. CBC obtained at 6 hours after reaction had increased neutrophils by 5000 cells/mm^3. She was discharged home with recommendation of continued strict avoidance of dietary CM protein and follow-up evaluation in 12 months.

Case 3. Feeding difficulties in an exclusively breast-fed infant with FPIES to multiple solid foods

A 10-month-old female infant has been exclusively breast-fed since birth without any formula supplementation. She has had 3 episodes of repetitive, projectile emesis that start within 2 hours after ingestion of rice cereal at 5 months of age, treated with intravenous fluid resuscitation in the ED. She has had similar but less severe emesis episodes with oatmeal and carrot. She has been given a diagnosis of FPIES and referred for diagnostic OFCs. She was recommended to add pear and sweet potato to her diet gradually at home, after negative SPTs to these foods. An office OFC had been done because her mother has been afraid to try these foods at home. The baby had refused these foods consistently, pushing away the spoon, gagging, and spitting up the contents. She also refused trying banana and apple. She was referred for a feeding evaluation. A trial of an elemental semisolid food was recommended at home to improve feeding skills.

BOX 1. Case presentations of FPIES.

Endoscopic evaluation

Endoscopy and biopsy are not routinely performed in classic FPIES. Endoscopies performed in infants with CM and/or soy FPIES revealed friable mucosa, rectal ulceration, and bleeding.[30] Biopsies showed variable villous atrophy; tissue edema; crypt abscesses; and increased lymphocytes, eosinophils, and mast cells.[11,25,27] Immunohistochemistry showed IgM- and IgA-containing plasma cells, increased TNF-α, and decreased TGF-β type 1 receptors.

Radiologic findings

Radiologic findings in infants with chronic diarrhea, rectal bleeding, and/or failure to thrive showed air-fluid levels, nonspecific narrowing and thumb-printing of the rectum and sigmoid, and thickening of the plicae circulares in the duodenum and jejunum with excess luminal fluid. If laparotomy was performed because of suspected ileus, distension of small bowel loops and thickening of the wall of jejunum distal to Treitz ligament with diffuse subserosal bleeding was reported.[32] These abnormal findings resolve with elimination of the trigger food.

OFCs

Although OFC is the "gold standard" for FPIES diagnosis, infants do not usually require confirmatory OFCs for initial diagnosis if they have a history of classic symptoms on multiple occasions or if hypotensive episodes and symptoms resolve after removal of the offending food from the diet. Physician-supervised OFCs are necessary, if the history is unclear or to determine whether FPIES has resolved before food reintroduction into the diet.[1]

Although initial diagnostic OFCs are not performed routinely, follow-up OFCs are necessary. Our conservative approach recommends follow-up OFCs every 18 to 24 months in patients without recent reactions.[20] Korean investigators recommended undertaking follow-up OFCs after 12 months for CM and between 6 and 8 months of age for soy because they showed that at 10 months 64% of infants tolerated CM and 92% tolerated soy.[33] More evidence from large studies is needed to establish the optimal timing of the follow-up challenges in FPIES.

Protracted emesis and dehydration necessitate fluid resuscitation in approximately 50% of reactive challenges. FPIES OFC is considered a high-risk procedure and should be conducted in a setting with available intravenous access and rapid fluid

resuscitation. Although an inpatient setting is preferable, an outpatient setting with resuscitation capabilities and access to a laboratory (for neutrophil counts and stool analysis) is sufficient. It remains to be determined whether oral rehydration can be used for patients with mild symptoms as reported in one study.[5] In our practice, a peripheral intravenous line is placed before starting an OFCs (Box 1, Case 2). OFCs are performed by administering food, 0.15 to 0.6 g protein/kg body weight, in 3 equal doses every 15 minutes.[34] A lower dose, 0.06 g protein/kg body weight, is used in patients with a history of severe reactions.[10,23] Table E3 (in this article's Online Repository at www.jaci-inpractice.org) provides a practical example of how to calculate and administer the food dose for an OFC. The total amount of food protein should not exceed 3 to 6 g or 10 to 20 g of total food weight or 100 mL of total liquid. Before an OFC, the possibility of an IgE-mediated reaction needs to be evaluated because a different dosing regimen should be used in this case.[23] If the lower initial dose was administered because of a history of severe reactions and no symptoms develop in 2 to 3 hours, an age-appropriate serving is usually given as a second feeding, followed by observation for approximately 4 hours. If no acute symptoms occur, patients are discharged home after 4 hours and advised to eat the food regularly. The OFC for FPIES is a long procedure, and appropriate staffing is needed to assure surpervision and observation during the OFC and period after OFC. The diagnostic criteria for a positive OFC, as originally proposed by Powell,[28] include (1) emesis and/or diarrhea, (2) fecal blood, (3) fecal leukocytes, (4) fecal eosinophils, and (5) increase in peripheral polymorphonuclear leukocytes count of >3500 cells/mm^3. Challenge is considered positive if 3 or more criteria are met, equivocal if 2 criteria are met, and negative if 1 or none criteria are met. A complete blood count with differential should be sent before and 6 hours after a symptomatic episode. Stool samples should be sent for occult heme, leukocyte, red blood cell, and eosinophils. On the basis of the more recent published evidence[2,5] and our own clinical practice, we suggest modification of the current diagnostic criteria to put major emphasis on emesis, which is the most constant feature reported and observed during an OFC. The proposed modified criteria would accept a positive FPIES OFC if repetitive emesis occurred within 30 to 240 minutes after food ingestion in the absence of skin or respiratory allergic symptoms. Supportive minor clinical criteria include diarrhea, abdominal pain, hypotension, lethargy, and suggestive laboratory findings of increased white blood count, fecal blood, fecal leukocytes, and fecal eosinophils.

DIFFERENTIAL DIAGNOSIS

FPIES differential diagnosis is extensive and includes infections (viral or bacterial gastroenteritis, sepsis), food poisoning, anaphylaxis, allergic proctocolitis and enteropathy, necrotizing enterocolitis, ileus, metabolic disorders, and congenital methemoglobinemia. The differential diagnosis is presented in greater detail in Table E4 (in this article's Online Repository at www.jaci-inpractice.org).

MANAGEMENT

Acute management

Treatment of acute FPIES includes intravenous fluids (10-20 mL/kg boluses of isotonic saline) for more severe episodes and oral rehydration fluids for mild episodes if tolerated.[5,11] A single dose of intravenous steroid, methylprednisolone 1 mg/kg, maximum of 60 to 80 mg, is recommended for reactions that include severe repetitive emesis, profuse diarrhea, lethargy, hypotension, and/or hypothermia to reduce the presumed cell-mediated intestinal inflammation.[20] Most reactions respond well to fluids and methylprednisolone. For severe hypotension, vasopressors may be necessary. Epinephrine should be available for shock; however, epinephrine does not improve symptoms of emesis and lethargy (authors' experience).[21] Bicarbonate for acidemia and methylene blue for methemoglobulinemia can be administered. Similar treatment is administered in chronic FPIES with dehydration. The patient should be re-hydrated with either oral or intravenous fluids; bicarbonate and methylene blue can be administered as needed. Temporary bowel rest and parenteral nutrition may be necessary in the most severe cases.

Because the clinical presentation and management of FPIES are unfamiliar in urgent care centers, it is helpful to provide patients with a letter, explaining the symptoms and management of acute reactions. A template of such a letter can be accessed online[20] at http://download.journals.elsevierhealth.com/mmcs/journals/0091-6749/PIIS0091674904024881.mmc1.pdf.

Long-term management

Management should be individualized, considering the reaction history and severity, specific IgE results, age of the child, and number and type of foods involved.

Strict allergen avoidance. Management consists of strict avoidance of the trigger food. Although patients with FPIES react to larger food amount (82% to >30-50 mL[5]), it is difficult to assess the patient's threshold dose because of delayed onset. Because of this and the fact that threshold dose may get smaller with repeated episodes, it is important to strictly avoid trigger food.[18] Extensively hydrolyzed casein formulas are recommended instead of soy-based formula because of the possibility of concomitant CM and soy FPIES. If soy-based formula is chosen, a soy OFC is recommended. Amino acid formula is needed in approximately 10% to 15% of the infants. In severe cases, temporary bowel rest and intravenous fluids may be necessary. Ingestion of cooked forms of foods is not recommended, based on the presumed T-cell involvement, because high temperature does not destroy sequential allergenic epitopes recognized by T cells. However, in one report, patients with CM FPIES tolerated cooked forms of milk.[35] More studies are needed to determine whether cooked foods could be tolerated by patients with FPIES.

Breast-feeding. Exclusive breast-feeding appears to protect against FPIES. Until recently, FPIES was reported only in formula-fed infants. Two reports were published of FPIES after ingesting breast milk because of a maternal intake of CM intake and soy.[6,7] However, among an additional 21 breast-fed infants with acute FPIES, only 3 mothers removed the trigger food from their diet; no FPIES episodes were reported in the 18 infants. IgE-mediated urticaria and anaphylaxis to foods ingested by breast-feeding mothers have been reported in infants.[36,37] Because FPIES is less common, reactions during exclusive breast-feeding might have been underreported. Small amounts of protein transferred to breast milk may be insufficient to meet the threshold dose, which is higher for FPIES than for IgE-mediated allergy.[38] The amounts passed to breast milk vary significantly among mothers[36]; the protein is partially digested and processed. For these reasons, the causative food should only be removed

from the maternal diet if reactions after breast-feeding occur or if the infant is failing to thrive.

Introduction of new foods. No controlled studies are available on food introduction in FPIES, and these recommendations are empirical, based on limited, existing data and our own experience (see Table E5 in this article's Online Repository at www.jaci-inpractice.org). Any food already tolerated by an infant should not be restricted. Yellow fruits and vegetables instead of cereal at 6 months of age have been suggested. If tolerated, grains, legumes, and poultry can be introduced to the diet.

Because of a high rate of multiple foods in solid foods FPIES, it may therefore be beneficial to avoid grains, legumes, and poultry in the first year of life because of the high likelihood of reacting to multiple foods.[10,20] Introduction of CM and soy in these infants may be attempted after 1 year of age, preferably under physician supervision, if there is no prior history of reactivity to these foods. Tolerance to one food from each high-risk group, for example, soy for legumes, chicken for poultry, or oat for grains, increases the likelihood of tolerance to other foods from the same group.[20]

Re-introduction of trigger food. The culprit food should be considered for reintroduction to the diet 12 to 18 months after the last reaction, in a physician-supervised setting.

Nutritional management. Considering the potential severity of the acute episodes as well as strict avoidance requirement, nutritional counseling should be offered to most patients with FPIES. Infants with multiple food FPIES are particularly vulnerable to nutritional deficits and feeding difficulties (Box 1, Case 3). Breast-fed young infants with reactions to first solid foods introduced to their diet may develop feeding difficulties. Food refusal may be related to past unpleasant experiences with solid food and can be magnified by parental apprehension. Counseling parents about strategies for enhancing feeding and oral skills is critical in these infants.

NATURAL HISTORY

Resolution of FPIES varies widely among reports from different countries, which may depend on the nature of the population studied (general vs referral) and the frequency of coexisting atopic diseases.[5,10,23,29,33] Table E3 summarizes the studies on the natural history for different foods (see Table E6 in this article's Online Repository at www.jaci-inpractice.org). For CM and soy, reports from Korea and Israel show overall more favorable prognosis compared with the US studies.[5,10,23,33]

Most children with FPIES have negative SPTs and undetectable serum food-specific IgE at diagnosis. Sicherer et al[23] observed that children with detectable food-specific IgE tend to have a more protracted course and are at risk of developing IgE-mediated immediate-type symptoms, which was recently also reported by Onesimo et al.[39] Therefore, including SPTs and/or measurement of serum food-specific IgE levels in the initial as well as follow-up evaluations is prudent to determine timing and the type of OFCs.

CONCLUSIONS

FPIES is a non—IgE-mediated food allergy that predominantly affects infants and young children. Diagnosis is based on the history, symptoms, exclusion of other causes, and, if necessary, an OFC. FPIES is frequently misdiagnosed because of nonspecific presentation that mimics acute viral gastrointestinal disease or sepsis, absence of classic allergic cutaneous and respiratory symptoms, the common misbelief that foods such as rice and oat are incapable of triggering allergic reactions, and lack of a biomarker. Early recognition of FPIES and removal of the offending food are imperative to prevent recurrent acute episodes and failure to thrive. CM and soy FPIES resolve in most patients by 3 years of age, and close follow-up is required to determine when OFCs are appropriate to assess for tolerance development. Patients with solid food FPIES and/or detectable food-specific IgE levels may have more protracted courses. Further research should focus on the pathophysiology and natural history of FPIES, as well as the unique diagnostic tools for initial diagnosis and monitoring of tolerance development.

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TABLE E1. Features of FPIES

Feature	Acute FPIES	Chronic FPIES
Triggering foods	Any food; most common CM, soy, and rice	CM and soy
Age at onset	Any; most cases start younger than 1 year, but fish and shellfish FPIES may start at any age	Within first year of life
Age at resolution	Variable, population-dependent, many cases resolve by 3 years of age	Variable, population-dependent; CM-FPIES resolution by 3 years of age ranges from 30% in referral population to 100% in unselected populations
Symptoms	Repetitive (up to 20 episodes), projectile emesis with onset in 1-3 hours after food ingestion, lethargy, pallor and ashen-gray appearance, diarrhea with blood and mucous in 2-10 hours after food ingestion, hypothermia, dehydration, hypotension, shock	Intermittent emesis, bloody diarrhea, poor weight gain or weight loss, abdominal distension, irritability, lethargy, pallor, dehydration, hypotension, shock
Laboratory blood tests	Elevated white blood count with left shift, thrombocytosis, methemoglobinemia, acidosis	Elevated white blood count with left shift and eosinophilia, anemia, hypoalbuminemia, low total protein, acidosis, methemoglobinemia
Fecal studies	Blood, mucous, sheets of leukocytes and eosinophils, and increased carbohydrate content	Occult blood, polymorphonuclear neutrophils, eosinophils, Charcot-Leyden crystals, and reducing substances
Radiologic studies	Intramural gas may be seen on abdominal x-rays	Air-fluid levels, nonspecific narrowing, and thumb-printing of the rectum and sigmoid, and thickening of the plicae circulares in the duodenum and jejunum with excess luminal fluid
Endoscopy and biopsy	Endoscopy: friable mucosa with rectal ulceration and bleeding Biopsies: varying degrees of villous atrophy; tissue edema; crypt abscesses; and increased lymphocytes, eosinophils, and mast cells	Same
Management	Trigger food elimination Fluid resuscitation Single dose of methylprednisolone for more severe reactions Bicarbonate for acidosis Methylene blue for methemoglobinemia	Trigger food elimination Fluid resuscitation Bicarbonate for acidosis Methylene blue for methemoglobinemia Temporary bowel rest with intravenous feeding
Allergy evaluation	Prick skin tests and serum specific IgE antibodies to offending food(s) usually negative	Same

TABLE E2. Comparison of clinical presentation of food protein-induced enterocolitis between reports from different continents

Study design and clinical features	Mehr 2009[E1] Australia (n = 66)	Sopo 2012[E2] Italy (n = 66)	Hwang 2008[E3] Korea (n = 16)
Design	Retrospective	Retrospective	Prospective CM OFC
Trigger foods	CM, soy, and solids	CM, soy, and solids	CM
Vomiting (1-3 h), %	100	98	87.5
Lethargy, %	85	—	62.5
Pallor/ashen-gray appearance, %	67	80	Not reported
Diarrhea (6-10 h), %	24	54	44
Temperature <36°C, %	24	Not recorded	Not recorded

TABLE E3. FPIES OFC preparation and calculation of the amount of food protein and the actual food administered for a child weighing 10 kg for two different dosing protocols developed at the Jaffe Food Allergy Institute at the Mount Sinai School of Medicine, New York, NY

	Actual food amount	
	Dose of 0.15 g protein/kg	**Dose of 0.6 g protein/kg**
Milk powder, nonfat	4.2 g	16.6 g
Milk liquid, nonfat	44 mL†	176 mL
Yogurt*, nonfat		
Soy Dream	51 mL	203 mL
Infant rice cereal	22.5 g	90 g
Infant oat cereal	11.25 g	45 g
Lean ground beef	5.7 g	22.8 g
Chicken breast	5.5 g	22 g
Sweet potato	75 g home cooked equals 3.75 ounces stage 1 pureed infant food‡	Normal serving size per age: 2-6 ounces§

Obtain current weight of the patient. Calculate the amount of food protein in grams per kilogram of body weight; range, 0.06 to 0.6; usual dosing, 0.15 to 0.3 g protein/kg body weight, up to a maximum of 10 g. Mix the amount calculated with a vehicle of choice, such as rice milk. Administer in 3 doses over 30 to 45 minutes.

*Nonfat yogurts have varying protein levels; must do calculation according to protein content of yogurt.

†As an example, add 44 mL of skim milk to rice milk for a total volume of 100 mL and administer in 3 doses over 30 to 45 minutes; 100 mL is used to simplify calculations. Total amount of food should be the smallest amount needed that will mask the challenge food and will be reasonable for the patient.

‡This may be more than an age-appropriate serving. The serving should be based on the child's age. Stage 1 serving size is 2.5 ounces, which provides 1 g of protein.

§Six grams of sweet potato protein is roughly the equivalent of 2 large sweet potatoes with an age appropriate serving of $^1/_4$ to $^1/_2$ cup.

TABLE E4. Differential diagnosis of FPIES

Condition	Distinction from FPIES
Gastrointestinal viral illness or food poisoning	Fever and sick contacts are typically present, emesis unrelated to ingestion of the same particular food
Sepsis	Antibiotics required for recovery
Anaphylaxis	Symptom onset acute (approximately 0.5-1 h), IgE-mediated symptoms that involve the skin or respiratory system are present, epinephrine helpful
Inborn errors of metabolism	Developmental delay, neurologic manifestations, organomegaly
Congenital methemoglobinemia	Cyanosis in an otherwise asymptomatic infant
Cardiovascular or neurologic disorders	Acute reaction on re-exposure to particular foods missing, gastrointestinal symptoms less prominent
Gastroesophageal reflux disease	Only upper intestinal symptoms are present
Intussusception	Intermittent, severe, crampy, progressive abdominal pain episodes
Hirschsprung disease	Characteristic delay in passage of the first meconium, fever, and abdominal distention
Necrotizing enterocolitis	Apnea or respiratory failure, prominent abdominal distention and tenderness present
Proctocolitis	Infant is typically well-appearing and thriving, exclusively breast-fed
Food protein-induced enteropathy	Acute reaction on re-exposure missing; vomiting less prominent; less severe presentation with no bloody diarrhea, methemoglobinemia, or acidemia
Eosinophilic gastroenteropathies	Acute onset (approximately 2 h) of gastrointestinal and systemic symptoms is missing, more often positive IgE tests and multiple food triggers

TABLE E5. Empirical recommendations for dietary management of FPIES

	Milk/soy FPIES	Solid food FPIES	Milk/soy and solid food FPIES
0-12 Months			
Avoid CM and soy	X		X
Exclusive breast-feeding* or extensively hydrolyzed casein formula† or consider soy OFC in case of milk FPIES	X		X
Introduce yellow vegetables	X	X	X
Avoid grains,‡ legumes, poultry		X§	X§
>12 Months			
Avoid trigger foods, OFC with reactive food every 18 months	X	X	X
Exclusive breast-feeding* or extensively hydrolyzed casein formula† or consider soy OFC in case of milk FPIES	X		X
Consider OFC with milk or soy if not tried	X	X	X
Consider OFC with grains, legumes, poultry if not tried		X§	X§

No controlled trials have been performed to determine optimal timing of introduction in infants and toddlers with FPIES.
*No maternal elimination diet recommended unless reactions to food through breast milk.
†If not tolerated, an amino acid-based formula should be initiated.
‡Includes oat, rice, wheat, barley, rye.
§OFCs may be necessary to introduce new solid foods to children with multiple food FPIES.

TABLE E6. Natural history of FPIES

	Country	Reference
CM		
60% resolution by 10 months of age	Korea	Hwang et al[E4]
90% resolution by 3 years of age	Israel	Katz et al[E5]
60% resolution by 3 years of age	United States	Nowak-Wegrzyn et al[E6] Sicherer et al[E7]
Soy		
90% resolution by 10 months of age	Korea	Hwang et al[E4]
25% resolution by 3 years of age	United States	Nowak-Wegrzyn et al[E6]
Solid foods		
48% resolution by 29 months of age: various foods	Italy	Sopo et al[E2]
67% resolution by 3 years of age: vegetables*	United States	Nowak-Wegrzyn et al[E6]
66% resolution by 3 years of age: oat*	United States	Nowak-Wegrzyn et al[E6]
40% resolution by 3 years of age: rice*	United States	Nowak-Wegrzyn et al[E6]

*These results are likely confounded because vegetables, rice, and oat are not essential to the diet and easy to avoid; therefore, many parents defer follow-up OFCs to these grains for their children.

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